REMARKS

Claims 27-34 are pending in this application.

Applicants respectfully traverse the present rejections.

Rejection under 35 U.S.C. § 101:

Claims 27-34 stand rejected under 35 U.S.C. §101 as allegedly not supported by either an asserted utility that is specific and substantial or by a well-established utility. Applicants respectfully disagree with the maintained rejection of claims 27-34 for the following reasons.

Applicants' asserted utility should be accepted because it is squarely within the teaching of leading textbooks in the field, and is supported by numerous references and the declarations of skilled experts. This evidence is sufficient to demonstrate utility because an applicant's evidence rebutting the Office's rejection for lack of utility does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility. In addition, the MPEP cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection is sustained only when the applicant asserted a utility "that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." MPEP § 2107.02 III B, citing *In re Gazave,* 379 F.2d 973 (CCPA 1967) (emphasis in original). Such is clearly not the case here. Moreover, **the PTO has recognized that Applicants' asserted utility is sufficient by issuing U.S. Patent No. 7,208,308 (the "'308 patent") with claims supported by the same utility as the utility asserted herein. *See, e.g.* Claim 1 of the '308 patent, which states that the claimed polypeptide is encoded by a nucleic acid that is amplified in lung or colon tumors.**

Issuance of the '308 patent is direct and persuasive evidence that Applicants' assertion of utility satisfies the requirements of 35 U.S.C. § 101. In particular, the protocols and

procedures of the gene amplification experiment in the '308 patent (Example 92) and the present application (Example 28) are identical. In addition, the ΔCt values resulting from these gene amplification experiments are similar: 1.0 – 3.82 ΔCt in the '308 patent vs. 1.05 to 3.51 ΔCt in the present application. Further, the Polakis and Scott Declarations submitted during prosecution of this application, and relied on by Applicants, also were submitted during prosecution of the '308 patent and accepted by the Office as evidence supporting the asserted utility. Indeed, the declaration of Randy Scott was submitted along with the response that led to issuance of the '308 patent.

The current Office action maintains rejection of the claims, and argues that the declarations and references cited by Applicants are not persuasive evidence of a utility for PRO357 because none of this evidence provides explicit data demonstrating that PRO357 is overexpressed as a polypeptide. Yet no such explicit data demonstrating that PRO343, claimed in the '308 patent, is overexpressed as a polypeptide is included in the '308 patent specification, nor was such provided during prosecution of the '308 patent, even though the asserted utility for the claimed PRO343 polypeptide is based on correlation between gene amplification and protein overexpression. Indeed, it is highly significant that in issuing the '308 patent, the PTO found the evidence submitted by the Applicants, including the declarations and references of record in this case, and the gene amplification data presented in the '308 patent specification, sufficient.

Moreover, contrary to the assertion in the Office action that, '[t]here is a complete absence of data supporting the statements which set forth the desired results of the claimed invention," page 3 of the Office action mailed March 7, 2007, the data in the present application is similar to the data presented in the '308 patent specification. Specifically, as discussed above and as in the issued '308 patent, the present application sets forth the ΔCt values for PRO357. A ΔCt value of at least 1.0 was observed for PRO357 in 26 of the tested tumors and tumor cell lines listed in Table 9. Indeed, PRO357 showed gene amplification of approximately 1.05 to 3.51 ΔCt units, which corresponds to $2^{1.05}$ to $2^{3.51}$ fold amplification in primary lung and colon tumors and tumor cell lines. These values demonstrate a significant amplification of the

PRO357 DNA. Applicants previously submitted a declaration of Audrey Goddard, Ph.D. demonstrating that one of ordinary skill in the art considers a ΔCt value greater than 1 to be significant and useful as a diagnostic marker. *See* paragraph 7 of the Goddard Declaration. Further, the ΔCt values for PRO357 correspond to the ΔCt values supporting the claims issued in the '308 patent (1.0 – 3.82 ΔCt in the '308 patent vs. 1.05 to 3.51 ΔCt in the present application). These ΔCt data values demonstrate that PRO357 is significantly amplified in approximately 93% of lung tumor tissues and approximately 75% of colon tumor tissues listed in Table 9.

Moreover, the data in the present application is also supported by the declarations of Paul Polakis and Randy Scott and by the references previously submitted by Applicants in support of their assertion of utility. This same evidence also was submitted in support of the claims issued in the '308 patent. The Office action alleges that the Polakis and Scott Declarations are not persuasive because those declarations do not contain any information specific to PRO357 mRNA expression or PRO357 polypeptide expression. However, Applicants respectfully submit that the Polakis and Scott Declarations are persuasive evidence supporting Applicants' assertion of utility when viewed in the proper context. Specifically, according to the Office action, the first factor to consider when determining whether declaratory evidence is persuasive is "the nature of the fact sought to be established." According to the Office action, "[t]he nature of the fact to be established is whether PRO357 polypeptide expression is elevated in tumors." Applicants respectfully disagree that this is the proper context for viewing the Polakis and Scott Declarations. Rather, the nature of the fact sought to be established in these declarations is that under the proper utility standard, which only requires a fact be more likely true than not, the gene amplification observed for PRO357 more likely than not correlates to overexpression of the PRO357 polypeptide. This fact is adequately established and supported.

Specifically, although Dr. Polakis works for the assignee of the present application, he still is a qualified expert. Dr. Scott is an independent qualified expert with no affiliation with the assignee of this patent application. As to factual support for the opinions of

these experts, the Second Polakis Declaration provides sufficient factual data to support Dr. Polakis's opinion as stated in his first and second declarations. Specifically, Exhibit B of the Second Polakis Declaration identifies 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Similarly, Dr. Scott unequivocally confirms that, as a general rule, there is a good correlation between mRNA and protein levels in a particular tissue. This conclusion, which states a general rule observed over time is based on the stated facts that Dr. Scott has more than 15 years experience with microarray technologies, and in his experience, Dr. Scott has noticed a good correlation. Indeed, Applicants note that the Scott Declaration was submitted along with the response that led to issuance of the '308 patent. Accordingly, the Polakis and Scott Declarations do support Applicants' assertion of utility and provide significant evidence that Applicants' assertion of utility satisfies the utility standard.

In addition, although there may be some opposing evidence, Applicants have cited substantial evidence supporting their assertion of utility. Indeed, issuance of the '308 patent, which has claims supported by the exact same utility as the utility asserted herein, is direct and persuasive evidence demonstrating that the PTO has accepted Applicants' assertion of utility.

Further, the majority of the art references cited and discussed during prosecution demonstrate that gene amplification is art recognized to correlate with mRNA levels and polypeptide expression levels. The Office action disagrees and argues that Pennica, Orntoft, Hyman, Pollack and Godbout are evidence that the claimed invention is not supported by an adequate utility. Applicants respectfully disagree. The Office action incorrectly dismisses Pennica as support for the asserted utility because allegedly Pennica provides evidence that DNA amplification is **not always** associated with

overexpression of the gene product. But the law does not require that the asserted utility be based on a correlation that "always" occurs; it only must be more likely to occur than not. Pennica, and the other references discussed below, meet this standard. In particular, for 2 of 3 genes studied, Pennica reported positive correlation between gene amplification and protein overexpression. Pennica also reported that the data showing that the expression levels of the third gene did not positively correlate with protein overexpression levels might be inaccurate. *See* Pennica at 14722. Thus, Pennica discloses that a good correlation was shown between gene amplification and protein overexpression for at least 2 of the 3 genes studied.

Similarly, according to the Office action, Orntoft is evidence that gene amplification does not always correlate with overexpression. Yet Orntoft reports that **in general** (18 of 23) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Orntoft *et al.,* in "Genome-wide study of gene copy numbers, transcripts, and protein levels in pairs of non-invasive and invasive human transitional cell carcinomas." 2002. *Molecular & Cellular Proteomics 1.1,* 37-45. The data presented in the specification demonstrates that PRO357 has a more than 2-fold gain of DNA in 93% of the lung tissues and 75% of the colon tissues tested and reported in Table 9.

The Office action states that Hyman reports only a 44% correlation which does not establish the correlation is more likely than not. But Hyman reports observing evidence of a **prominent global influence of copy number changes on gene expression levels**. *See* Hyman *et al.,* "Impact of DNA amplification on gene expression patterns in breast cancer." 2002. *Cancer Research*, 62:62-40-6245. Similarly, Pollack reports that **on average**, a 2-fold change in DNA copy number was associated with a corresponding 1.5 fold change in mRNA levels. Pollack *et al.,* "Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors." 2002. *PNAS,* 99(20):12963-12968.

According to the Office action, Godbout *et al.* is relevant because it teaches co-amplified genes are only overexpressed if they provide a selective advantage. Applicants respectfully disagree that Godbout teaches that amplified genes are *only* overexpressed if they provide a selective advantage. Rather, Godbout, which focuses on *co-amplified* genes, states that "it is unlikely that a gene located ~ 400 kb from the *MYCN* gene will be consistently amplified as an intact unit unless its product provides a growth advantage to the cell." Page 21162 of Godbout. Thus, rather than conclude that an amplified gene must encode a polypeptide that provides a selective advantage, Godbout suggests that the selective advantage plays a role in why a particular gene may be co-amplified with another gene. Applicants further respectfully submit that this aspect of the Godbout teachings is not relevant to Applicants' assertion of utility, which is not based on any gene that is alleged to be co-amplified. Further, Applicants note that regardless of the co-amplification aspect of the Godbout reference, this reference teaches that a DEAD box gene, DDX1, shows good correlation between gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cancer cell lines studied. *See* pages 21164, 21167, and 21168. Thus, Godbout does not teach that Applicants assertion of utility is wholly inconsistent with or violates any scientific principles nor does Godbout make it more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of utility.

Thus, Applicants respectfully submit that when the evidence of the references is taken as a whole, as it must be, that evidence demonstrates that in general it is more likely than not that there is a correlation between gene amplification and protein overexpression. For example, the Ziang reference cited by Applicants and discussed in the Office action demonstrates this correlation. In addition, the teachings of Alberts (Molecular Biology of the Cell) and Lewin (Genes) disclose that initiation of transcription is the most common point for a cell to regulate the gene expression but the Office action rejects these references because they do not teach anything explicitly related to PRO357 and because these references also acknowledge such is not the only means of regulating gene expression. Yet, these references should not be rejected because, according to PTO standards of demonstrating utility, which only requires that the

asserted utility is more likely than not true, not necessarily true, Applicants have demonstrated an adequate utility.

Thus, as recognized by the PTO in issuing U.S. Patent No. 7,208,308, gene amplification is an essential mechanism for oncogene activation and in general gene amplification more likely than not correlates with protein overexpression. In the present case then, it is more likely than not that the gene amplification demonstrated for PRO357 correlates with protein overexpression of PRO357. This is sufficient to satisfy the utility requirement, particularly because consideration of the totality of the evidence clearly demonstrates that Applicants' asserted utility is specific, substantial, and credible. Applicants have overcome this ground of rejection and respectfully request it be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph:
Enablement

The Examiner contends that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. Applicants respectfully disagree. As discussed above, the claimed invention is adequately supported by an asserted utility that is both specific and substantial. Applicants respectfully request the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112 ¶1 for alleged inadequate disclosure on how to use the claimed invention.

Claim Rejections under 35 U.S.C. § 102(b)

The Office action rejects claims 27-34 under 35 U.S.C. § 102(b) as being anticipated by Botstein *et al.* (WO 99/35170, published 7/15/99). Anticipation under 35 U.S.C. § 102(b) requires that "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, *more than one year prior to the date of application for patent in the United States.*"

An application for a patent based on the present invention was filed at least as early as December 22, 1998, which is prior to the publication date of the cited reference. In particular, the PRO357 polypeptide and amino acid sequences are disclosed in U.S. Provisional Application Serial No. 60/113,296 ("the '296 application"), filed 12/22/1998. More specifically, the nucleic acid sequence encoding PRO357 is identified as DNA44804 and is shown in Figure 15 (SEQ ID NO:15) of the '296 application. This sequence corresponds to Figure 25 (SEQ ID NO:68) in the present application. The amino acid sequence encoding PRO357 is shown in Figure 16 (SEQ ID NO:16) of the '296 application, which corresponds to Figure 26 (SEQ ID NO:69) in the present application. In addition, the gene amplification experiment described in Example 28 of the present specification is described in Example 2 of the '296 application. For the reasons discussed above, description of the gene amplification assay in the '296 application satisfies the utility and enablement requirements.

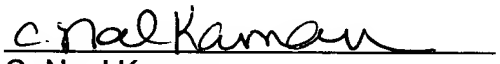
As an application for a patent based on the present invention was filed at least as early as December 22, 1998, Applicants respectfully submit that rejection of claims 27-34 under 35 U.S.C. § 102(b) based on the Botstein reference (WO 99/3517, published 7/15/99) is improper and respectfully request that this ground of rejection be withdrawn.

CONCLUSION

Applicants believe this Request for Reconsideration fully responds to the Office Action. Applicants respectfully request the Examiner grant allowance of claims 27-34. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite this application.

Applicants believe no fee is due in connection with the filing of this Request for Reconsideration, however, should any fees be deemed necessary for any reason relating to this paper, the Commissioner is hereby authorized to deduct said fees from Brinks Hofer Gilson & Lione Deposit Account No. 23-1925. A duplicate copy of this document is enclosed.

Respectfully submitted,



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